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(54) Title: SYNERGISTIC COMBINATION COMPRISING ROFLUMILAST AND AN ANTICHOLINERGIC AGENT SELECTED FROM IPRATROPIUM, OXITROPIUM AND TIOTROPIUM SALTS FOR THE TREATMENT OF RESPIRATORY DISEASES

(57) Abstract: The invention relates to the administration of roflumilast oral or untravenously and an anticholinergic agent selected from the group of an ipratropium, oxitropium or tiotropium salt for the treatment of respiratory diseases.

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SYNERGISTIC COMBINATION COMPRISING ROFLUMILAST AND AN ANTICHOLINERGIC AGENT SELECTED FROM IPRATROPIUM, OXITROPIUM AND TIOTROPIUM SALTS FOR THE TREATMENT OF RESPIRATORY DISEASES

Field of application of the invention

The invention relates to the combination of certain known active compounds for therapeutic purposes. The substances used in the combination according to the invention are a known active compound from the PDE inhibitor class and active compounds from the anticholinergic agent class.

Prior art

International patent applications WO02/069945 and WO03/011274 generally describe the combination of a compound from the class of PDE4 inhibitors with a compound from the class of anticholinergic agents for the treatment of respiratory tract disorders. International Patent application WO02/096463 describes an inhaled combination of a selective PDE4 inhibitor and an anticholinergic agent, with the proviso that the anticholinergic agent is not a tiotropium salt. International patent application WO02/096423 describes a combination of therapeutic agents useful in the treatment of obstructive airways and other inflammatory diseases comprising (I) a PDE4 inhibitor that is therapeutically effective in the treatment of said diseases when administered by inhalation; together with (II) an anticholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof that is therapeutically effective in the treatment of said diseases when administered by inhalation. In the US patent application No. US2002/0052312 a method for the treatment of chronic obstructive pulmonary disease is described comprising administering orally to a patient in need of such treatment a therapeutically effective amount of a muscarinic receptor antagonist in combination with a therapeutically effective amount of at least one other therapeutic agent selected from the group consisting of: β2-agonist, antitussive, corticosteroid, decongestant, histamine H1 antagonist, dopamine antagonist, leukotriene antagonist, 5-lipoxygenase inhibitor, phosphodiesterase IV inhibitor, VLA-4 antagonist, and theophylline.

Summary of the invention

The invention relates to pharmaceutical products and methods for preventing or reducing the onset of symptoms of respiratory diseases, or treating or reducing the severity of respiratory diseases. In particular it relates to compositions and methods for treating respiratory diseases mediated by phosphodiesterase 4 (PDE4) by administering a PDE4 inhibitor together with another pharmaceutically active agent, which affects pulmonary function. In this connection, it is the object of the present invention to make available a certain respiratory tract therapeutic, which fulfills the following conditions:

- Pronounced antiinflammatory action
- Distinct bronchorelaxation and -dilatation
- Good bioavailability
- Minor side effects
- Good suitability for long-term therapy
- Favorable influence on bronchial hyperreactivity

It has now been found that the combined use of the orally or intravenously administered PDE4 inhibitor roflumilast and the administration by inhalation of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts outstandingly fulfills the abovementioned conditions, in particular in view of the fact that the combination of the compounds acts synergistically, i. e. exhibits a greater than additive effect.

Accordingly, the invention relates in a first aspect to a method for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease by administering to a patient in need thereof in succession, close in time or remote in time, in any order whatever to a patient in need thereof (1) an effective amount of roflumilast orally or intravenously and (2) an effective amount of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts by inhalation.

The invention also relates to a pharmaceutical product for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease, comprising as a free combination

(a) an effective amount of roflumilast in a formulation suited for oral or intravenous administration and
(b) an effective amount of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts in a formulation suited for administration by inhalation.

Detailed description of the invention

The combination therapy which is the subject matter of this invention comprises administering roflumilast with an anticholinergic agent selected from the group of ipratropium, oxitropium or tiotropium salts to prevent onset of a respiratory disease event or to treat an existing condition.

According to the invention, the two compounds are administered in different dosage forms. The selective PDE4 inhibitor roflumilast is administered orally or intravenously, while the anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts is administered by inhalation. The two compounds of the combination according to the invention may be administered at the same

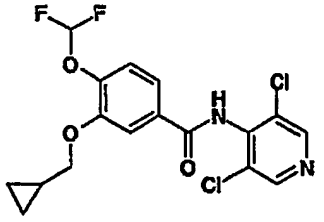
time; or they may be administered sequentially, i.e. the compounds are administered one after the other (close in time or remote in time).

The combination may be used prophylactic or after the onset of symptoms has occurred. In some instances the combination may be used to prevent the progression of a respiratory disease or to arrest the decline of a function such as lung function.

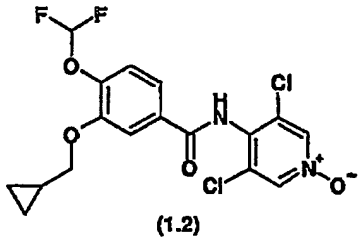
The invention thus relates to the combined use of roflumilast and an anticholinergic agent selected from the group of ipratropium, oxitropium or tiotropium salts, preferably ipratropium bromide, oxitropium bromide or tiotropium bromide in preventing the symptoms of, or treating a respiratory disease.

In the sense of the invention, the term "roflumilast" is understood to include the pharmaceutically acceptable salts and the N-oxide of ROFLUMILAST, which can likewise be used according to the invention.

ROFLUMILAST is the international nonproprietary name (INN) for 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide [structure of formula (1.1)]. The preparation of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide, its pharmaceutically acceptable salts and its N-oxide [3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxypyrid-4-yl)-benzamide; structure of formula (1.2)] as well as the use of these compounds as phosphodiesterase (PDE) 4 inhibitors is described in WO95/01338.



(1.1)

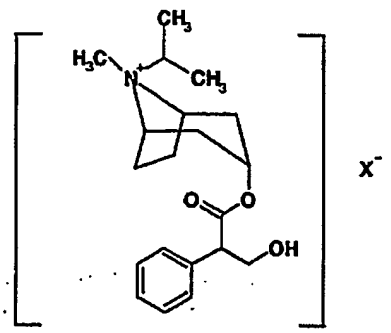


(1.2)

Suitable pharmacologically acceptable salts of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST) are in particular water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-naphthoic acid, the acids being employed in salt preparation – depending on whether it is a mono- or polybasic acid and depending on which salt is desired – in an equimolar quantitative ratio or one differing therefrom.

Anticholinergic agents suitable for use in the invention are ipratropium, oxitropium or tiotropium salts.

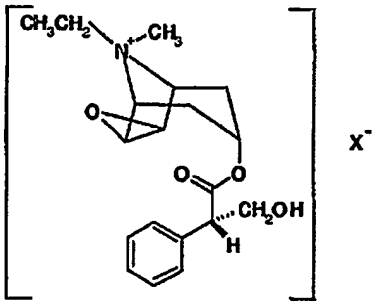
An ipratropium salt (see DE1670142) has the structure of formula (1.3)



(1.3)

wherein X is a pharmaceutically acceptable anion.

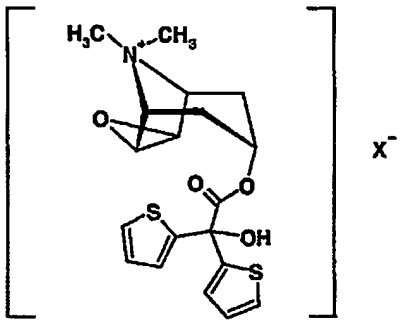
An oxitropium salt (see DE1795818) has the structure of formula (1.4)



(1.4)

wherein X is a pharmaceutically acceptable anion.

A tiotropium salt (see EP 418716, WO02/051840) has the structure of formula (1.5):



(1.5)

wherein X is a pharmaceutically acceptable anion.

Examples of suitable salt forms of ipratropium, oxitropium and tiotropium are fluoride, F^- chloride, Cl^-; bromide, Br^-; iodide, I^-; methanesulfonate, $CH_3S(=O)_2O^-$; ethanesulfonate, $CH_3CH_2S(=O)_2O^-$; methylsulfate, $CH_3OS(=O)_2O^-$; benzene sulfonate $C_6H_5S(=O)O^-$; and para-toluenesulfonate, $4\text{-}CH_3\text{-}C_6H_5S(=O)2O^-$. The bromide salt form is preferred.

Preferred combinations for use in the invention include:

- roflumilast and an ipratropium salt, particularly ipratropium bromide
- roflumilast and an oxitropium salt, particularly oxitropium bromide
- roflumilast and a tiotropium salt, particularly tiotropium bromide or tiotropium bromide monohydrate

It is understood that the active compounds and their pharmaceutically acceptable salts mentioned can also be present, for example, in the form of their pharmaceutically acceptable solvates, in particular in the form of their hydrates. Of particular importance in this connection is tiotropium bromide in form of its crystalline monohydrate as disclosed and described in detail in WO02/30928. The preparation of crystalline water-free tiotropium bromide is described in WO03/000265. An alternative process for the preparation of tiotropium bromide is described in WO02/051840.

Respiratory diseases which may be mentioned are in particular allergen- and inflammation-induced bronchial disorders (bronchitis, obstructive bronchitis, spastic bronchitis, allergic bronchitis, allergic asthma, bronchial asthma, COPD), which can be treated by the combination according to the invention also in the sense of a long-term therapy (if desired with appropriate adjustment of the dose of the

individual components to the needs at the time, for example needs subject to seasonally related variations). The combination is particularly useful in the treatment of COPD.

"Combined use" or "combination" within the meaning of the present invention is to be understood as meaning that the individual components are administered (from separate pack units) at the same time or in succession, close in time or remote in time, in any order whatever. As an example, the two active compounds could be taken one after the other; or one active compound could be taken in the morning and one later in the day. In a further scenario, one active compound could be taken twice daily and the other once daily, either at the same time as one of the twice-a-day dosing occurred, or separately.

"Combined use" or "combination" within the meaning of the present invention is particularly to be understood as meaning that the two active compounds act together in a synergistic manner.

Within the meaning of the present invention, "use" is to be understood as meaning with respect to roflumilast the oral or intravenous administration. The oral administration can be accomplished, for example, in form of tablets, coated tablets, capsules, caplets, emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and where by appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form exactly suited to the desired onset of action can be achieved. The intravenous administration is accomplished customarily in form of aqueous solutions, optionally containing suitable co-solvents. Preferred is the oral administration of roflumilast.

The person skilled in the art is familiar with auxiliaries and/or excipients, which are suitable for the desired oral or intravenous pharmaceutical formulations of roflumilast on account of his/her expert knowledge. In addition to solvents other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

With respect to the anticholinergic agents, "use" in accordance with the invention is to be understood to mean administration by inhalation. As suitable administration forms for inhalation may be mentioned, for example, inhalation powders, propellant-containing aerosols and propellant-free inhalation solutions.

The anticholinergic agents of the present invention may be conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrodynamics to produce a fine mist) or nebulizer, with or without the use of a suitable propellant, e. g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,2,2-tetrafluoroethane (HFA 134A [trade mark]) or,

1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide, a further perfluorinated hydrocarbon such as Perflubon [trade mark] or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered dose. The pressurized container , pump, spray, or nebulizer may contain a solution or suspension of the anticholinergic agent, e. g. using a mixture of ethanol (optionally aqueous ethanol) or a suitable agent for dispersing, solubilizing or extending release and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules, blisters and cartridges (made, for example, from gelatin or HMPC) for use in an inhaler or insufflator may be formulated to contain a powder mix of anticholinergic agent of the invention, a suitable powder base, such as lactose or starch and a performance modifier such as l-leucine, mannitol or magnesium stearate.

Prior to use in a dry powder formulation for inhalation an anticholinergic agent of the invention will be micronised to a size suitable for delivery by inhalation (typically considered as less than 5 microns). Micronisation could be achieved by a range of methods, for example spiral jet milling, fluid bed jet milling or use of supercritical fluid crystallization.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine-mist may contain from 1 µg to 10 mg of an anticholinergic agent of the invention and the actuation volume may vary from 1 to 100 µl. A typical formulation may comprise an anticholinergic agent of the invention, propylene glycol, sterile water, ethanol and sodium chloride.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 4000 µg of an anticholinergic agent of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range from 1 µg to 20 mg which may be administered in a single dose or, alternatively, in divided doses throughout the day.

With respect to tiotropium bromide or tiotropium bromide monohydrate suitable tiotropium-containing powdery preparations for inhalative administration are disclosed in the international applications WO02/30389 and WO03/084509. In the international application WO02/098874 inhalation capsules (inhalettes) containing the active agent tiotropium in the form of a powder preparation are disclosed. Propellant-free inhalation formulations of tiotropium bromide or tiotropium bromide monohydrate are disclosed in the international applications WO02/36104 and WO02/36591. Aerosol formulations, free of propellant gas, comprising a pharmaceutically acceptable salt of tiotropium dissolved in water are disclosed in the international application WO03/084519. Methods for the production of micronized crystalline tiotropium bromide are disclosed in WO03/078429.

For the above-mentioned prophylactic and therapeutic uses the dosages administered will, of course vary with the first and second active compound employed, the treatment desired and the disorder indicated.

The active compounds are dosed in an order of magnitude customary for the individual dose, it more likely being possible, on account of the individual actions, which are mutually positively influencing and reinforcing, to reduce the respective doses on the combined administration of the active compounds compared with the norm.

For inhalation, ipratropium bromide is administered in a dose of preferably 1 to 3 mg per day by once, twice, three or four times daily administration; oxitropium bromide is administered in a dose of preferably 0.2 to 0.6 mg per day by once, twice or three times daily administration; tiotropium bromide monohydrate is administered in a dose of 10 to 25 µg, preferably 22.5 µg per day by once daily administration.

In the case of the oral administration of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST) the daily dose is in the range from 100 to 500 µg per day, preferably by once daily administration.

In the case of the intravenous administration of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST) the daily dose is in the range from 50 to 500 µg per day, preferably in the range from 150 to 300 µg.

Preparation Examples:

There follows a description of several Examples showing preparation of pharmaceutical compositions containing a combination of active compounds in accordance with the present invention. These examples are intended to further illustrate the combinations of active compounds of the present invention, pharmaceutical compositions containing them and processes in accordance with which said pharmaceutical compositions may be readily prepared by a person skilled in the art. The person skilled in the art will be aware of many other suitable processes and pharmaceutically acceptable carriers that are also available, as well as acceptable variations in the procedures and ingredients described below.

Example 1: ROFLUMILAST Tablets

ROFLUMILAST is mixed with the first portion of corn starch and, subsequently, triturated in a planetary mill. The trituration is screened (1.0 mm sieve) and transferred into the product container of a fluidised bed granulator. Microcrystalline cellulose, sodium carboxymethylstarch (type A) and the second portion of corn starch are added to the product container. A solution of povidone in purified water is sprayed onto the powders under suitable process conditions until granules of a suitable size range

are obtained. The granules are dried to the moisture content specified. Magnesium stearate is added to the dried granules using a suitable mixer. The blend is compressed into tablets having an average weight of approx. 60 mg using a standard rotary tablet press. Each tablet contains 250 µg of ROFLUMILAST.

Example 2: Tiotropium Bromide monohydrate Dry Powder Inhaler (mono dose system based on capsule for inhalation)

0.225 g of micronized tiotropium bromide monohydrate and 49.8 g lactose monohydrate are mixed in a turbula mixer in two steps. The blend is screened (0.71 mm sieve) to break up any agglomerates and, subsequently, transferred into the container of a planetary mixer. After adding additional 200.0 g lactose monohydrate and mixing, 25 mg of the blend are filled into hard gelatin capsules size #3 using a capsule filling machine. The capsules can be administered with a commercially available inhaler, e.g., the Cyclohaler®. One capsule contains 22.5 µg of tiotropium bromide monohydrate.

Pharmacology

Inhibition of Methacholine-induced Bronchoconstriction in Guinea Pigs by ROFLUMILAST in combination with tiotropium-bromide

Objective

To assess the inhibitory effect of tiotropium-bromide, ROFLUMILAST, and the combination of both compounds on methacholine-induced bronchoconstriction in anaesthetized, mechanically ventilated guinea pigs.

Animals

Male Dunkin Hartley-guinea pigs; body weight 350-450 g when performing the experiments.

Experimental procedure

75 min before methacholine-induced bronchospasm (at –75 min) animals were anaesthetized with urethane i.p. (1.2 g/kg). At –55 min for i.v. injections the right jugular vein and for ventilation the trachea was cannulated. At –45 min NaCl 0.9% or tiotropium-bromide was administered i.v. (1 µg/kg). At –30 min lactose (10 mg/kg) or ROFLUMILAST (4 mg/kg) mixed with lactose was administered intratracheally by a dry powder aerolizer. At –10 min pancuronium-bromide (1.5 mg/kg) was administered i.v. to abolish spontaneous breathing. Animals were mechanically ventilated with 60 breath/min and a tidal volume of 7 ml/kg. Dynamic lung compliance (COM) and airway conductance (CON) were calculated with the help of a computer system from airflow and ventilation pressure signals. At t=0 min methacholine was administered i.v. (60 µg/kg) to induce bronchoconstriction.

Analysis of lung physiology data

COM and CON were determined up to 120 s after methacholine-induced bronchospasm. AUCs for 0 to 120s were determined. Inhibition was calculated based on the AUC data. Data are shown as mean ± SEM. Results were taken to be significant if $p<0.05$ versus placebo (ANOVA and Dunnett's multiple comparison test)

Results

Injection of methacholine induced an immediate bronchoconstriction characterized by a decrease of COM and CON; maximum at 20 s (Fig.1 and Fig. 2).

Pretreatment with ROFLUMILAST had no significant effect on methacholine-induced bronchospasm (Fig. 1 – 4, COM –1.6 %, CON 5.6 %).

Pretreatment with tiotropium-bromide had no significant effect on methacholine-induced bronchospasm (Fig. 1 – 4, COM 12 %, CON 5.9 %).

Combination of both treatments led to an unexpected synergistic significant ($p<0.01$) inhibition of methacholine-induced COM decrease (Fig. 1 and 3, COM 41 %) and CON decrease (Fig. 2 and 4, CON 25 %, $p<0.05$).

Conclusion

Whereas ROFLUMILAST and tiotropium-bromide alone had no influence on methacholine-induced bronchospasm in aneasthetized and mechanically ventilated guinea pigs, combination of both active compounds showed an unexpected synergistic inhibition.

Description of the Figures:

Figure 1: Methacholine induced compliance decrease in guinea pigs

Figure 2: Methacholine induced conductance decrease in guinea pigs

Figure 3: AUC Compliance 0-120 s

Figure 4: AUC Conductance 0-120 s

Patent claims

1. A pharmaceutical product for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease, comprising as a free combination
(a) an effective amount of roflumilast in a formulation suited for oral or intravenous administration and
(b) an effective amount of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts in a formulation suited for administration by inhalation.

2. A pharmaceutical product according to claim 1 for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease, comprising as a free combination
(a) an effective amount of roflumilast in a formulation suited for oral administration and
(b) an effective amount of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts in a formulation suited for administration by inhalation.

3. A pharmaceutical product according to claim 1 for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease, comprising as a free combination
(a) an effective amount of roflumilast in a formulation suited for intravenous administration and
(b) an effective amount of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts in a formulation suited for administration by inhalation.

4. A pharmaceutical product according to claim 1, 2 or 3 wherein the anticholinergic agent is tiotropium bromide or tiotropium bromide monohydrate.

5. A pharmaceutical product according to claim 1, 2 or 3 wherein the anticholinergic agent is ipratropium bromide.

6. A pharmaceutical product according to claim 1, 2 or 3 wherein the anticholinergic agent is oxitropium bromide.

7. A pharmaceutical product according to any one of claims 1 to 6, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide.

8. A pharmaceutical product according to any one of claims 1 to 6, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxypyrid-4-yl)benzamide.

9. A method for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease by administering simultaneously or sequentially, close in time or remote in time, in any order whatever to a patient in need thereof (1) an effective amount of roflumilast orally or intravenously and (2) an effective amount of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts by inhalation.

10. A method according to claim 9 for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease by administering simultaneously or sequentially, close in time or remote in time, in any order whatever to a patient in need thereof (1) an effective amount of roflumilast orally and (2) an effective amount of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts by inhalation.

11. A method according to claim 9 for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease by administering simultaneously or sequentially, close in time or remote in time, in any order whatever to a patient in need thereof (1) an effective amount of roflumilast intravenously and (2) an effective amount of an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts by inhalation.

12. A method according to claim 9, 10 or 11, wherein the two active compounds are administered sequentially, close in time or remote in time, in any order whatever.

13. A method according to claim 9, 10, 11 or 12 wherein the anticholinergic agent is tiotropium bromide or tiotropium bromide monohydrate.

14. A method according to claim 9, 10, 11 or 12 wherein the anticholinergic agent is ipratropium bromide.

15. A method according to claim 9, 10, 11 or 12 wherein the anticholinergic agent is oxitropium bromide.

16. A method according to any one of claims 9 to 15, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide.

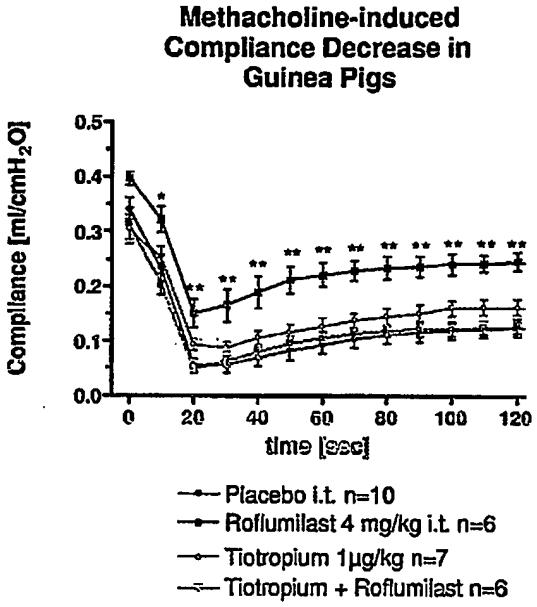
17. A method according to any one of claims 9 to 15, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxypyrid-4-yl)benzamide.

18. A method according to any one of claims 9 to 17, wherein the respiratory disease is COPD.

19. Medicament pack, containing (a) roflumilast as active ingredient in a formulation suited for oral or intravenous administration and (b) a description that roflumilast can be administered, for reducing the

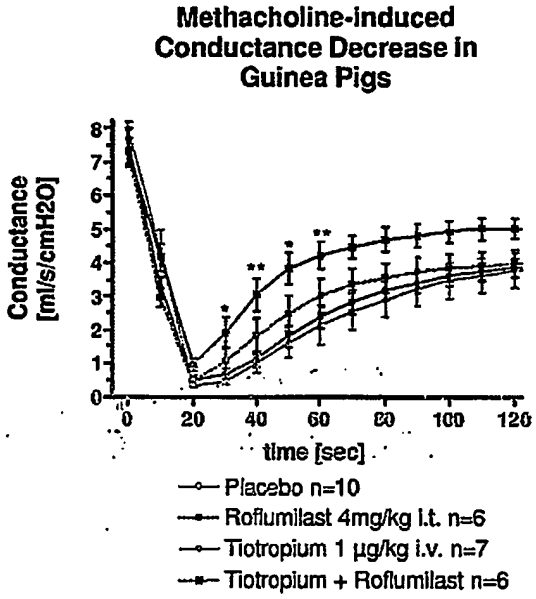
onset of symptoms of a respiratory disease, or for treating or reducing the severity of a respiratory disease together with an anticholinergic agent selected from the group of ipratropium, oxitropium and tiotropium salts in a formulation suited for administration by inhalation, sequentially, where the sequential adminstration is close in time or remote in time and in any order whatever.

Figure 1



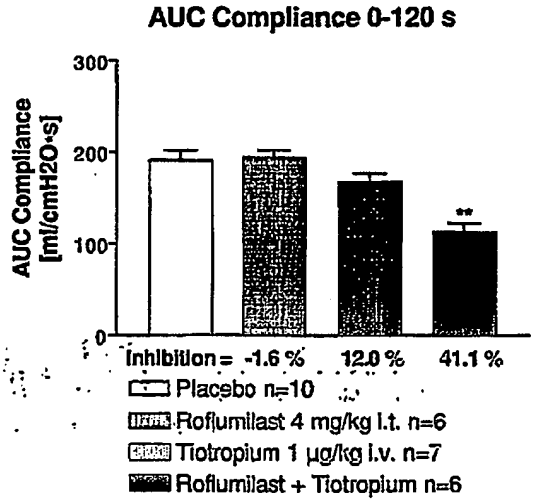
Data are shown as mean ± SEM. *p<0.05, **p<0.01 vs. placebo

Figure 2



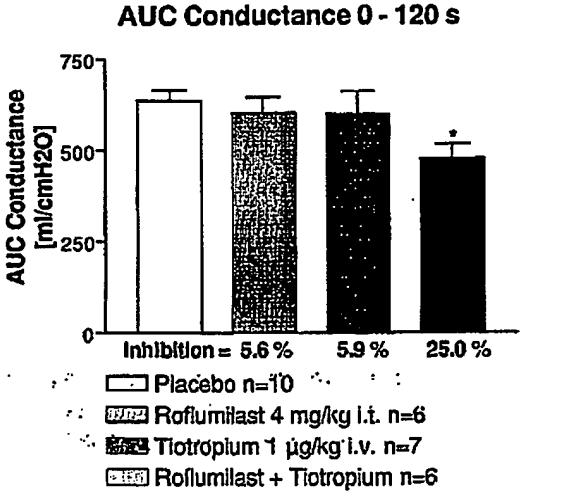
Data are shown as mean ± SEM.*p<0.05, **p<0.01 vs. placebo

Figure 3



Data are shown as mean ± SEM. **p<0.01 vs. placebo.

Figure 4



Data are shown as mean ± SEM. *p<0.05 vs. placebo.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050377

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/46 A61K31/44 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 03/011274 A (GLAXO GROUP LTD ;WARD PETER (GB); KNOWLES RICHARD GRAHAM (GB)) 13 February 2003 (2003-02-13) page 6, lines 8-12; claims 1,5-9 page 4, line 25 page 5, lines 19-23	1,2, 4-10, 12-19 3,11
Y	WO 02/069945 A (BOEHRINGER INGELHEIM PHARMA ;PIEPER MICHAEL PAUL (DE); PAIRET MICH) 12 September 2002 (2002-09-12) cited in the application claims 1-5,9,35	1-19
Y	US 2002/052312 A1 (BACH MARK A ET AL) 2 May 2002 (2002-05-02) paragraph '0024!; claims 1,11 paragraph '0039!	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2004	02/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allnutt, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/050377

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-18 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/050377

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		US	2002193393 A1	19-12-2002
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US 2002052312 A1	02-05-2002	NONE		